BIOLOGICS

(Dollars in Thousands)	FY 2018 Enacted	FY 2018 Actual	FY 2019 Annualized CR	FY 2020 President's Budget	FY 2020 +/- FY 2019 Annualized CR
Biologics	**363,766**	**381,890**	**379,144**	**431,561**	**52,417**
Budget Authority	***217,138***	***217,135***	***217,138***	***262,138***	***45,000***
User Fees	***146,628***	***164,755***	***162,006***	***169,423***	***7,417***
Center	320,146	338,310	335,355	387,812	52,457
Budget Authority	175,132	175,131	175,132	220,132	45,000
User Fees	145,014	163,179	160,223	167,680	7,457
Prescription Drug (PDUFA)	*130,171*	*151,195*	*144,529*	*151,782*	*7,253*
Medical Device (MDUFA)	*13,602*	*11,887*	*14,444*	*14,117*	*-327*
Generic Drug (GDUFA)	*1,055*	*78*	*1,072*	*1,085*	*13*
Biosimilars (BsUFA)	*186*	*19*	*178*	*696*	*518*
Field	43,620	43,580	43,789	43,749	-40
Budget Authority	42,006	42,004	42,006	42,006	---
User Fees	1,614	1,576	1,783	1,743	-40
Prescription Drug (PDUFA)	*1,410*	*1,370*	*1,566*	*1,532*	*-34*
Medical Device (MDUFA)	*204*	*206*	*217*	*211*	*-6*
FTE	**1,434**	**1,434**	**1,394**	**1,422**	**28**

Authorizing Legislation: Public Health Service Act; Federal Food, Drug, and Cosmetic Act; Medical Device Amendments of 1976; Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 201); Safe Medical Devices Act of 1990; Medical Device Amendments of 1992; Food and Drug Administration Modernization Act of 1997; Medical Device User Fee and Modernization Act of 2002; Public Health Security and Bioterrorism Preparedness Response Act of 2002; Project Bioshield Act of 2004; Medical Device User Fee Stabilization Act of 2005; Food and Drug Administration Amendments Act of 2007 (FDAAA); Patient Protection and Affordable Care Act of 2010; Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA); Drug Quality and Security Act of 2013; Pandemic and All-Hazards Preparedness Reauthorization Act of 2013; 21st Century Cures Act of 2016 (Cures Act); Food and Drug Administration Reauthorization Act of 2017 (FDARA) (P.L. 115-52).

Allocation Methods: Direct Federal/Intramural

PROGRAM DESCRIPTION AND ACCOMPLISHMENTS

The Biologics Control Act, passed in 1902, established the Biologics Program in the Department of Treasury's Hygienic Laboratory, which later became part of the National Institutes of Health (NIH) in 1930. In 1972, the Biologics Program was transferred from NIH to FDA and became the Bureau of Biologics. In 1988, the Bureau became the Center for Biologics Evaluation and Research (CBER) which, with the Office of Regulatory Affairs' (ORA) biologics field program, comprises the FDA Biologics Program.

The mission of CBER is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, allergenics, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through its mission, CBER also seeks to protect the public against the threats of emerging infectious diseases and bioterrorism. CBER uses sound science and regulatory expertise to:

- Protect and improve public and individual health in the United States and, where feasible, globally;
- Facilitate the development of, approval of, and access to safe and effective biological products and promising new technologies; and
- Strengthen CBER as a preeminent regulatory organization for biological products.

CBER's strategic plan contributes to the improvement of public health and provides a framework for how CBER can most effectively allocate its fiscal and human resources to navigate the challenges and opportunities of 21st Century medicine successfully. The CBER goals include:

- Increase the nation's preparedness to address threats as a result of terrorism, pandemic influenza, and emerging infectious diseases.
- Improve global public health through international collaboration including research and information sharing.
- Utilize advances in science and technology to facilitate development of safe and effective biological products.
- Ensure the safety of biological products.
- Advance regulatory science and research.
- Manage for organizational excellence and accountability.

The Biologics Program accomplishments align with the CBER and Department of Health and Human Services' Strategic Plan, the FDA 2018 Strategic Policy Roadmap, and reflects implementation of new legislative mandates, expanded roles in addressing health needs, recent innovations in regulatory science and technology, and expanded opportunities for collaboration. The following selected accomplishments demonstrate the Biologics Program's delivery of its regulatory and public health responsibilities within the context of current priorities.[48]

Foster Competition and Innovation

FDA takes steps to facilitate efficient access to beneficial, safe and effective, and innovative products that can address existing, novel, and emerging health problems. FDA's Biologics Program is committed to helping to expedite the development and review of new biological products for a broad range of complex and life-threatening diseases. The program seeks to advance the development of innovative and complex biological products, including those representing ground breaking treatments, the exciting medical promise of precision medicine, and treatment options where very limited options exist. FDA also promotes innovation in manufacturing that can increase the reliability and safety of product supply, ensure the domestic supply of strategic biologics products, and potentially lower the cost of products through advances in how they are made.

Modernizing the Regulatory Process to Improve Innovation

FDA is taking steps to ensure the regulatory process is predictable, transparent, and scientifically modern, while also facilitating innovation by applying a risk-based regulatory approach. FDA has developed new policies and guidance for product regulation in key areas of novel medical science, with the goal of creating pathways that allow beneficial new technologies to efficiently reach patients while maintaining our standards for product safety and effectiveness. This work to modernize the regulatory process supports the strategy from the HHS Strategic Plan FY 2018-

[48] Please visit http://www.fda.gov/ for additional program information and detailed news items

2022 to leverage cutting-edge science to support product development strategies and regulatory evaluation.

Programs such as the Regenerative Medicine Advance Therapy (RMAT) Designation, Fast Track, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review are used when appropriate to expedite the development and review of innovative biological products. Since the inception of the Breakthrough Therapy Designation process in July 2012, CBER has granted 40 Breakthrough Therapy designations, with 28 of the 40 products being for rare diseases (Orphan Product designated). In FY 2018, FDA granted seven Breakthrough Therapy designations. The Agency has also granted 30 RMAT Designations since program inception in December 2016[49].

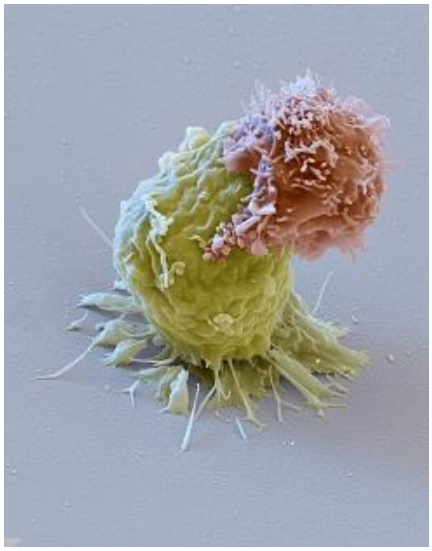

Figure 5 CAR-T Cell Attacking Cancer Cell

The FDA's 2017 approvals of the first three gene therapy products, two that use engineered immune T-cells to reprogram a patient's own cells to attack cancer and one directly administered gene therapy, are a result of decades of research. To support continued innovation in this field and provide clear recommendations to sponsors and researchers of novel therapies, FDA issued a suite of six human gene therapy guidances in July 2018. These guidances serve as the building blocks of a modern, comprehensive framework to help advance the field of human gene therapy while making sure new products meet the FDA's standards for safety and effectiveness. Three guidances are disease specific (hemophilia, retinal disorders and rare diseases) and three provide comprehensive updates to three existing guidances, originally published from 2006 and 2008, that address manufacturing issues related to human gene therapy.

FDA is working with the National Institute of Standards and Technology and other stakeholders to facilitate an effort to coordinate and prioritize the development of standards and consensus definitions of terms for regenerative medicine therapies, which include gene therapies. These standards and terms will help foster the development, evaluation, and review of such products.

FDA launched the INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meeting program in June 2018 for potential sponsors to engage with FDA early in the development process and obtain advice on a wide range of development-related topics. These meetings can be used to clarify CBER's expectations regarding product development programs and to help facilitate more efficient product development.

Ensure Availability of Novel Products

To improve innovation and help unlocking the full potential of novel technologies like cell and gene therapies, and new vaccines, FDA is working with industry on advanced manufacturing technologies. These technologies hold great promise for improvements in the reliability, flexibility and cost effectiveness of manufacturing for biological products. CBER awarded five grants to globally-recognized research institutions to study and recommend improvements for the continuous manufacturing of biological products, as well as innovative monitoring and control

[49] As of December 31, 2018

techniques. These grants help encourage the establishment of high tech manufacturing platforms in the U.S. and help bridge the knowledge and experience gaps in the adoption of emerging manufacturing technologies in the biological product sector.

FDA works to ensure the domestic supply of certain strategic products. For CY 2018, the Biologics Program has documented four new drug product shortages, 14 prevented shortages, five ongoing shortages, 44 notifications from 22 different manufacturers. CBER has used regulatory flexibility to prevent or mitigate one shortage and expedited 19 reviews to prevent or mitigate a shortage.

FDA developed a work plan in 2018 with the U.S. Department of Defense (DoD) to ensure that those products that are prioritized by DoD as important to the health of those involved in national defense receive the highest level of attention from the Agency, on par with breakthrough designated therapies. The plan was finalized, and a MOU was signed, in November 2018. This plan enhances collaboration and coordination and places initial priority on products regulated by CBER to help ensure safe and effective products are available to those protecting our Nation.

In July 2018, FDA granted an emergency use authorization (EUA) to DoD to enable the emergency use of Pathogen-Reduced Leukocyte-Depleted Freeze-Dried Plasma. Under this EUA, the product is authorized for the treatment of hemorrhage or coagulopathy of U.S. Military personnel during an emergency involving agents of military combat when plasma is not available for use or when the use of plasma is not practical. Hemorrhage is the leading cause of preventable deaths among combat trauma casualties.

To further advance the development and availability of dried plasma, in October 2018, FDA issued a draft guidance titled, "Considerations for the Development of Dried Plasma Products Intended for Transfusion." The draft includes recommendations regarding starting materials for the preparation of dried plasma products, manufacturing and product quality, product characterization studies, packaging and reconstitution, clinical studies and devices for manufacturing dried plasma.

Real World Evidence to Evaluate Effectiveness and Safety

In December FDA released a new strategic approach, "the Framework for the Real-World Evidence Program," to leverage information from large medical databases from healthcare providers, insurance claims data, and other partners. FDA is developing new tools to collect data from routine medical care to gain a deeper understanding of a medical product's safety and benefits, additional treatment implications, and potential limitations. Real-World Evidence (RWE) captured throughout the totality of a product's post-approval lifecycle has been a significant aid in informing regulatory decisions, including the development of new products and changes to existing products. This initiative ties to the strategy from the HHS Strategic Plan FY 2018-2022 to identify and assess adverse events related to the use of regulated human medical products, including the development and more effective use of large, nationally representative database systems, electronic health records, common data models, and natural language processing (NLP).

FDA continued progress in launching the Biologics Effectiveness and Safety (BEST) Initiative, an expansion of the CBER Sentinel program. BEST provides access to electronic health record sources from over 20 million patients to conduct robust, rapid safety/effectiveness studies of blood, advanced therapeutics and vaccines. Though the BEST Initiative, CBER has successfully

implemented improved coding for biological products with three data partners, vastly improving our transfusion safety surveillance capabilities.

BEST has been used to perform several hundred queries related to safety and regulatory questions such as estimating blood usage, identifying reasons for transfusions, and identifying transfusion-related adverse events and estimating their rates. Leveraging the power of BEST, FDA developed individual clinical profiles for transfusion recipient patients and estimated adverse event rates for transfusion-related acute lung injury across three data partners for the period of spanning 2010 to 2018.

Further, BEST is harnessing innovative approaches such as machine learning, artificial intelligence and NLP to conduct queries and medical chart reviews of EHR records to improve FDA's ability to identify cases of Transfusion-Associated Circulatory Overload and Post-transfusion Sepsis, both very serious and life-threatening medical conditions.

FDA collaborated with the Center for Medicare and Medicaid Services to conduct a rapid response analysis of the relative effectiveness of cell-cultured and egg-based vaccines among Medicare beneficiaries ages greater than 65 years of age. This investigation showed a modest increase in effectiveness of cell-cultured vaccines as compared to egg-based vaccines.

FDA, in collaboration with the National Heart Lung and Blood Institute and the HHS Office of the Assistant Secretary launched the Transfusion Transmissible Infections Monitoring System (TTIMS) to help assure the continued safety of the U.S. blood supply and monitor the effects of FDA's policy changes regarding donor deferral. TTIMS contractors are actively monitoring over 60 percent of the U.S. blood supply by developing methods to calculate incidence/prevalence for HIV, hepatitis B virus and hepatitis C virus pre- and post-implementation of the men who have sex with men one-year donor deferral policy.

The contractors completed recency testing of all in-house HIV samples on 8.4 million blood donations collected from January 2017 through September 2018 by the American Red Cross. It was determined and reported at the 2018 AABB conference that it is too early to understand the impact of the blood deferral policy, since the number of donations from reinstated MSM donors (0.017 percent of the 8.4 million donations) is too small to assess any meaningful impact on national blood collections.

Improve Global Public Health Through International Collaboration

FDA provides scientific and regulatory advice to sponsors and stakeholders and collaborates with other agencies and international regulatory authorities such as NIH/National Institute of Allergy and Infectious Diseases, HHS, the Biomedical Advanced Research and Development Authority, and the Coalition for Epidemic Preparedness Innovations on prevention of emerging infectious diseases. International collaborations enable a rapid/effective response to public health emergencies using established communication channels, relationships, partnerships. Rapid response helps decrease the spread of infectious disease, which may be spread by travel to endemic areas.

In October 2018, FDA/CBER representatives participated in the World Health Organization (WHO) Expert Committee on Biological Standardization meeting to establish WHO Biological Reference Preparations and written standards relevant to the manufacturing, licensing, and control of biological products. FDA also participated with the Management Committee and

Assembly of the International Council for Harmonisation to discuss Multiregional Clinical Trials, Good Clinical Practices, and Continuous Manufacturing.

FDA collaborated with CDC and WHO to enable the availability of an investigational Ebola vaccine provided to individuals residing in the Democratic Republic of the Congo suffering from a current outbreak of this disease. In June 2018 CBER also participated in WHO's Global Advisory Committee for Vaccine Safety. This committee provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long-term national immunization programs.

FDA representatives serve as members of the WHO Blood Regulators Network, a forum for international blood regulatory authorities to share insights and address threats and opportunities to promote global blood product safety, efficacy and availability. FDA also served as the Chair to the Asia-Pacific Economic Cooperation Regulatory Harmonization Steering Committee to continue efforts around establishing Centers of Regulatory Excellence for training regulators in best regulatory practices.

FDA hosted the 21st U.S.-Japan Cellular and Gene Therapy Conference on March 1, 2018, in conjunction with Japan's Ministry of Education, Culture, Sports, Science and Technology, under the U.S.-Japan Cooperative Research Program. Ideas were exchanged on cutting edge and diverse areas of biomedical research, and enhanced opportunities for collaborations, focusing on neurodegenerative diseases, growing challenges, therapeutic advances and barriers to progress in the research area.

To yield greater efficiencies for U.S. and E.U. regulatory systems by avoiding duplication of inspections and enable reallocation of resources towards inspection of manufacturing facilities with potentially higher public health risks across the globe, FDA signed a Mutual Recognition Agreement with the European Union on November 1, 2017. CBER has actively participated in conducting assessments resulting in fifteen-member states achieving positive capability assessments and has begun requesting inspection reports for firms under its auspices.

Strengthen Science and Efficient Risk-Based Decision Making

To modernize our regulatory toolbox, FDA is incorporating the best science and implementing policies that help new, beneficial innovations reach consumers efficiently. By adopting the most advanced science and risk management tools to inform our policies, FDA will facilitate product development by designing better ways of predicting the safety, purity, potency, and effectiveness of biological products early in their life cycle. These tools will help maintain FDA's gold standard for product review, and make sure that our approach to managing risk are efficient and up-to-date.

FDA also ensures the continued safety of the blood and tissue supply by keeping them free of infectious agents and contamination and approving safe and effective vaccines to prevent the spread of infectious diseases. This work is instrumental in decreasing the morbidity and mortality associated with these diseases as well as helping to halt the spread of the disease.

FDA's field work plays an integral role in helping to assure the safety of FDA-regulated products. The field staff provides additional surveillance through inspections at domestic and foreign manufacturing facilities and clinical study sites, including blood and tissue establishments, vaccine and allergenic facilities, device manufacturers, gene and cell therapy facilities, and plasma fractionators. Strengthening science and efficient based decision making

supports the HHS strategic plan strategy to "Improve surveillance, epidemiology, and laboratory services" to guide better decision making to target interventions more responsibly, and ultimately improve health.

Facilitate Product Development Through Applied Research

Incorporating the best science is a key part of promoting access to products that can help people improve their lives. FDA contributes to, and draws on, advances in science and technology to design better ways of predicting the safety, purity, potency, and effectiveness of biological products early in their life cycle and to facilitate product development.

The Biologics Program has a cadre of scientific experts who understand the regulatory process and conduct research to address scientific gaps. The applied research program supports development of new tools, models, standards, and methods, harnessing new technologies to expedite product development and provide effective regulatory responses to public health emergencies. This work supports the strategy from the HHS Strategic Plan FY 2018-2022 to conduct research to facilitate development and availability of innovative, safe, and efficacious medical products, including development of regulatory science.

In October 2018, FDA with the Centers of Excellence in Regulatory Science and Innovation, held a workshop, "Predictive Immunogenicity for Better Clinical Outcomes." The workshop included discussion on the advances in the development of technological approaches for predictions of immunogenicity and explored strategies for choosing appropriate tools and interpreting the results. Immunogenicity, the propensity of a therapeutic protein to induce immune responses, may affect safety and/or efficacy, and is thus an important concern in the development and regulation of cell and gene therapies and protein therapeutics, which are rapidly expanding therapies.

In May 2018, CBER convened the Vaccines and Related Biological Products Advisory Committee to discuss approaches for demonstrating effectiveness of group B streptococcus (GBS) vaccines intended for use in pregnant women to protect the newborn infant. GBS causes substantial infant morbidity and mortality globally. The development, licensure, and distribution of an effective vaccine that protects against invasive GBS disease in the newborn and young infant would be expected to significantly reduce disease. Currently, there no licensed vaccine to prevent GBS disease, however research is emphasizing the development of a vaccine that can be administered to pregnant women to prevent infant disease.

In September 2018, FDA and NIH/ National Institute of Allergy and Infectious Diseases held a public workshop entitled, "Science and Regulation of Live Microbiome-Based Products Used to Prevent, Treat, or Cure Diseases in Humans" to bring together the scientific community to discuss microbiome-based products and how they may be used to prevent or treat a variety of different diseases. Topics included the regulatory framework for live microbiome-based products; safety and effectiveness of live microbiome-based products used to prevent, treat, or cure diseases in humans; and strain selection for live microbiome-based products to prevent, treat, or cure diseases in humans.

Many diseases that used to be common in this country and around the world, including polio, measles, diphtheria, pertussis, rubella, mumps, tetanus, rotavirus and Haemophilus influenzae type b can now be prevented by vaccination. Vaccines have eradicated smallpox and prevented countless cases of disease and saved millions of lives.

While vaccines are highly effective, there have been small increases in Mumps and pertussis in the United States. Research conducted in coordination with CDC indicates that by college age, levels of anti-mumps virus antibodies had declined substantially. FDA is currently evaluating ways of improving the vaccine, such as optimizing the structure of the vaccine virus to trigger the production of longer-lasting, more robust antibodies. To determine why pertussis rates have been rising, CBER is studying pertussis vaccine in baboons, an animal model that closely reproduces the way whooping cough affects people and found that people immunized with acellular vaccines may be protected from whooping cough symptoms, they may still become infected and infect others, including infants.

Modernizing Clinical Data to Make Product Development More Efficient

FDA has been working to modernize the approach to the design of clinical trials for drugs and biologics to help make drug development more efficient and less costly and to increase information for providers and patients. To help modernize the process FDA held two joint public meetings in March 2018 to help gather feedback for the development clinical trial guidance documents and new pilot programs.

Two draft guidances were released in September 2018. The first guidance gives recommendations to sponsors to address the design and conduct of clinical trials intended to evaluate more than one investigational drug at the same time, or more than one cancer type or both within the same overall trial structure. For example, a trial could allow multiple rare B-cell malignancies to be tested with one therapy. The second guidance addresses adaptive trial designs that allows for planned modifications to one or more aspects of the design based on data collected from the study's subjects while the trial is ongoing, to improve efficiency.

FDA launched two new pilots for drugs and biologics: Complex Innovative Designs (CID) Pilot Meeting Program and Model-Informed Drug Development (MIDD). CID helps to solidify the science used to support novel approaches and promote their adoption in drug development programs. MIDD approaches facilitate the development and application of exposure-based, biological, mathematical and statistical models derived from preclinical and clinical data sources and use a variety of quantitative methods to help balance the risks and benefits of drug products in development. These pilots will help further the development of medical products.

Protect the Public Health from Infectious Disease

Infectious diseases are not only spreading faster; they appear to be emerging more quickly than ever before. Since the 1970s, over 40 infectious diseases have been discovered which can be spread through contact with infected individuals, travel to endemic areas, arthropod vectors, risk behaviors, and many other mechanisms. According to the Centers for Disease Control and Prevention, vaccines, which are regulated by FDA to ensure they are safe and effective, have reduced preventable infectious diseases to an all-time low and now few people experience the devastating effects of vaccine-preventable diseases. The following graphic compares vaccine-preventable diseases in the U.S. from the 1900's to present time.[50]

[50]Source: Adapted from the CDC Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition https://www.cdc.gov/vaccines/pubs/pinkbook/index.html and the March 2018 update at https://www.cdc.gov/vaccines/pubs/pinkbook/pink-errata.html.

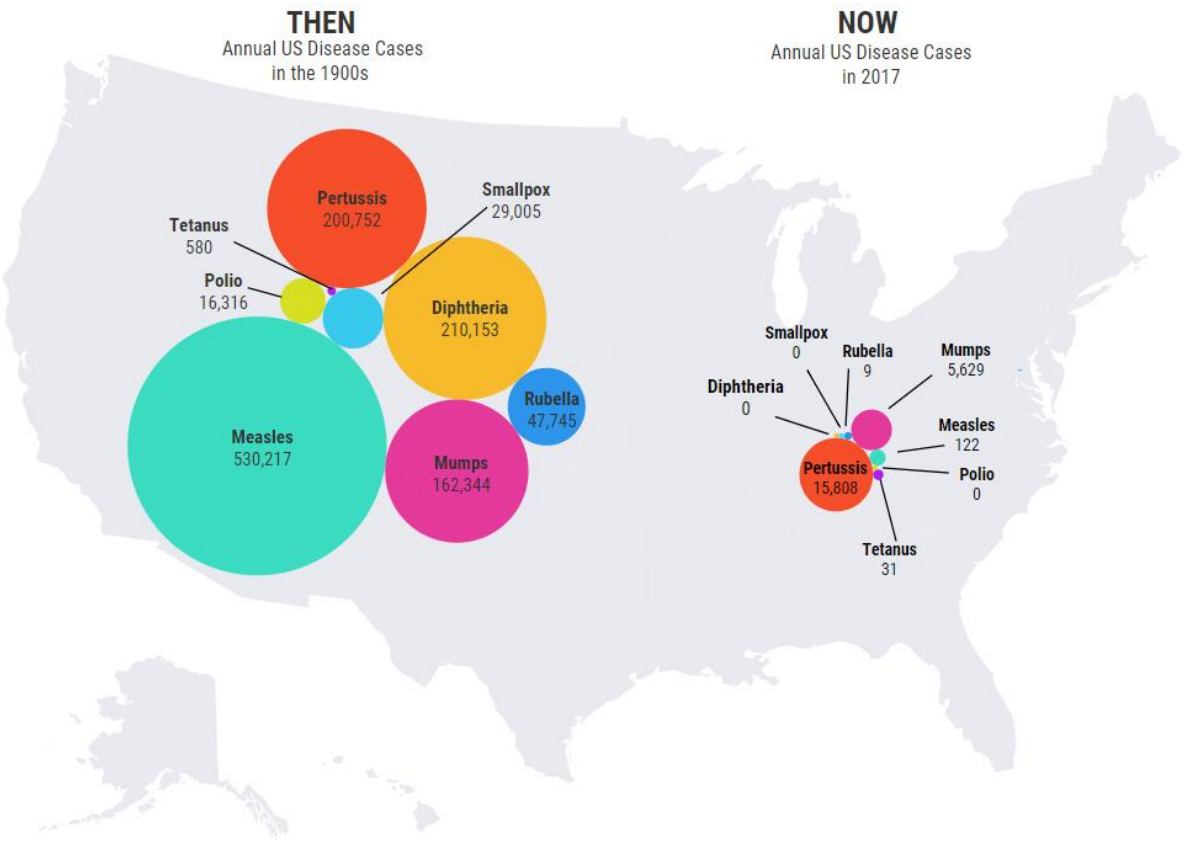

Figure 6 Impact of Vaccines in the 20th and 21st Centuries

FDA approved three influenza vaccines, expanding their approved use to include children as young as six months of age, in 2018. Previously only one influenza vaccine was approved for use in children as young as 6 months of age. Children younger than 5 years of age, especially those younger than 2 years, are at high risk of serious flu-related complications.

Each year, FDA, WHO, CDC and other public health experts collaborate on the review of influenza disease surveillance and laboratory data collected from around the world to identify influenza strains that may cause the most illness in the upcoming season. Based on this information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee, which met on March 1, 2018, FDA selected the strains for inclusion in the influenza virus vaccines for the 2018-2019 U.S. influenza season.

To promote the development and adoption of innovations that can ensure the continued safety of the U.S. blood supply, FDA released "Bacterial Risk Control Strategies for Blood Collections Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion" draft guidance in December 2018. The draft guidance incorporates feedback from discussions held during the July 2018 Blood Products Advisory Committee meeting and updates the previous draft guidance from 2016 and reflects broader FDA efforts to advance and encourage new developments to enhance product safety. This guidance also further advances the potential for technology to be used to reduce the risk of contamination of the blood supply from known and emerging pathogens, while ultimately reducing cost overall.

To ensure there are effective and efficient ways to screen for Zika in the blood supply, as well as in donated human cells and tissues, FDA published revised recommendations in July 2018 for testing blood donations for the Zika virus. When Zika virus first emerged, the unknown course of the epidemic and the observed severe effects from the disease indicated that individual donor testing was needed to ensure the continued safety of the blood supply. Given the significant decrease in cases of Zika virus infection in the U.S. and its territories, FDA now recommends testing pooled blood donations and switching to individual donor testing only in specific situations, based on guidelines in FDA published guidance.

Figure 7 Figure 3 Blood Donation

Current scientific knowledge continues to support the recommendation to screen living donors of cells or tissues for risks of infection with Zika virus based on geographical areas with risk.

FDA is working to protect the blood and tissue supply from tick-borne diseases; the Centers for Disease Control (CDC) has identified 18 tick-borne pathogens in the United States and additional pathogens associated with tick bites are emerging.

Transfusion-transmitted babesiosis has emerged as a significant risk to the U.S. blood supply. Human babesiosis is a disease transmitted primarily through tick vectors caused by Babesia microti (B. microti), which is a rodent parasite. In March 2018, FDA approved the first donor screening tests for the detection of antibodies to B. microti in human plasma samples and for the detection of B. microti DNA in human whole blood samples. In July 2018, FDA published a draft guidance providing recommendations for donor screening, donation testing, donor deferral, and product management to reduce the risk of transfusion-transmitted babesiosis from donors of blood and blood components. In January 2019, FDA approved the first nucleic acid amplification test (NAT test) for the detection of RNA from multiple Babesia species in whole blood specimens.

Pathogen reduction technology has the potential to improve blood safety by reducing or eliminating infectious organisms, including bacteria, viruses, and parasites, from blood components intended for transfusion. CBER continues to support the development and implementation of pathogen reduction technologies for blood components intended for transfusion. To help advance these technologies and explore expansion of their use from plasma and apheresis platelets for transfusion to whole blood and red blood cells, in November 2018, CBER hosted a two-day public workshop on Pathogen Reduction Technologies for Blood Safety.

Compliance and Oversight

Postmarket inspections are conducted after products are approved and help to ensure that the biologics industry continuously reviews the quality standards of its manufacturing operations to maintain the safety and effectiveness of biological products on the U.S. market. These inspections are performed to assure that products are manufactured in compliance with Current Good Manufacturing Practices and other applicable FDA regulations.

Surveillance is provided through inspections at domestic and foreign manufacturing facilities and clinical study sites, including blood and tissue establishments, vaccine and allergenic facilities, device manufacturers, gene and cell therapy facilities, and plasma fractionators. This work

supports the strategy from the HHS Strategic Plan FY 2018-2022 to "Improve surveillance, epidemiology, and laboratory services" to guide better decision making to target interventions more responsibly, and to identify and mitigate urgent and persistent threats to public health.

Though cell-based regenerative medicine holds significant medical promise, the marketing of unapproved treatments potentially puts patients' health at risk. As a part of FDA's comprehensive policy framework for the development and oversight of regenerative medicine products, FDA took action regarding three stem cell companies in 2018 for marketing products without FDA approval and for significant deviations from good manufacturing practice requirements, putting patients at risk. These actions included:

- Filing two complaints in federal court seeking permanent injunctions to stop two stem cell clinics from marketing stem cell products until, among other things, they obtain necessary FDA approvals and correct their violations of current good manufacturing practice requirements.
- Issuing a warning letter for marketing an adipose derived stem cell product without FDA approval and for significant deviations from current good manufacturing practice requirements.

EMPOWER CONSUMERS AND PATIENTS

FDA is also working to bridge early-stage efforts, such as the Patient Focused Drug Development meetings, to advance more systematic, methodologically-sound approaches to collect patient and caregiver input, such as burden of disease and treatment and the benefits and risks in the management of the patient's disease, so that it becomes data that can further inform regulatory decision-making.

In June 2018, CBER and CDER issued the draft guidance, "Patient-Focused Drug Development: Collecting Comprehensive and Representative Input." It is the first of a series of four patient-focused drug development guidance documents to address, in a stepwise manner, how stakeholders (patients, researchers, medical product developers and others) can collect and submit patient experience data and other relevant information from patients and caregivers for drug and biological product development and regulatory decision-making.

To inform development of patient-focused drug development guidance in October 2018, FDA hosted a workshop to identify methodological approaches to develop and identify what is most important to patients and caregivers; and best practices for selecting, developing or modifying fit-for-purpose Clinical Outcome Assessments to measure the patient experience in clinical trials.

CBER initiated three patient experience data studies to collect patient preference information to inform regulatory decision-making. Patients are the people who will ultimately experience the benefits, risks, and daily impact of disease treatments. Patients have diverse circumstances and experiences that shape their preferences and their willingness to accept risks in pursuit of treatments that bring benefits to their lives. As FDA weighs treatments for approval, it is important to understand how different patient populations balance the benefits and risks of different treatment options.

SELECTED GUIDANCES TO SUPPORT MISSION AND PRIORITY AREAS

FDA guidances are documents that explain the agency's interpretation of, or policy on, a regulatory issue. Guidances are prepared primarily for industry, but also for other stakeholders and internal staff, and FDA uses them to address such matters as the design, manufacturing, and testing of regulated products; scientific issues; content and evaluation of applications for product approvals; and inspection and enforcement policies. Although guidances are not legally binding, they show stakeholders one way to reach their regulatory goal. However, stakeholders are free to use other approaches that satisfy the relevant law and regulations.

Below are other selected guidance documents recently issued by CBER, not discussed elsewhere in the Biologics Program Description and Accomplishments.[51]

[51] Complete information on CBER guidances can be found at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances Complete information on CBER rules can be found at: http://www. fda. gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ActsRulesRegulations/default. htm

Date	#	Title	Description
Dec 2018	FDA-2018-D-3380	Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products; Draft Guidance	Describes considerations for the development and labeling of in vitro companion diagnostic devices to support indicated uses of multiple biologic oncology when appropriate.
Oct 2018	FDA-2018-D-3090	Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment; Draft Guidance	Assists sponsors planning to use minimal residual disease as a biomarker in clinical trials conducted under an investigational new drug application or to support marketing approval of biological products for treatment of specific hematologic malignancies.
Oct 2018	FDA-2018-D-3268	Rare Diseases: Early Drug Development and the Role of Pre-IND Meetings;Draft Guidance	Assists sponsors of biological products for the treatment of rare diseases in early development and in the planning of and participation in formal pre-investigational new drug application meetings with the FDA.
Sept 2018	FDA-2015-D-3438	Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use; Guidance	Provides industry FDA's recommendations on selection of appropriate package type terms and selection of appropriate discard statements for injectable medical products for human use, packaged in multiple-dose, single-dose, and single-patient-use containers.
Aug 2018	FDA-2018-D-3092	Hematologic Malignancy and Oncologic Disease: Considerations for Use of Placebos and Blinding in Randomized Controlled Clinical Trials for Drug Product Development; Draft Guidance	Provides recommendations to industry regarding use of placebos and blinding in randomized controlled clinical trials in development programs for biological products for treatment of hematologic malignancies and oncologic diseases.

SELECTED BIOLOGICS PRODUCT APPROVALS

New biological drugs such as vaccines, blood products, biotechnology products, and gene therapy and biological medical devices must be proven safe and effective before companies can put them on the market. FDA reviews the results of laboratory, animal, and human clinical testing done by companies to determine if the product they want to put on the market is safe and effective.

FDA's Biologics Program has reviewed and approved an array of biological products to treat and prevent diseases. Below are other selected recent Biological product approvals.

Disease	Approved	Trade Name	Proper Name	Purpose or Benefit
Certain cancers and diseases caused by nine HPV types	Oct 2018	Gardasil 9	Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant	Expanded the approved use of the vaccine to include women and men aged 27 through 45 years
Transfusion reactions	Oct 2018	ID CORE XT	ID CORE XT (Reagents and Analysis Software)	Red blood cell typing provides significant advantages to patients requiring frequent transfusions helping to reduce transfusion reactions.
Thermal Burn Wounds	Sep 2018	RECELL Autologous Cell Harvesting Device	Mechanical and enzymatic autologous skin processor for preparing cell suspension, with applicator	Covers up to 80 times the area of the donor skin sample. Sprayed onto a burn for patients 18 years of age and older.
Hemophilia A	Aug 2018	JIVI	Antihemophilic Factor (Recombinant), PEGylated	Used to treat and control bleeding in previously treated adults and adolescents (12 years of age and older) with hemophilia A.
Zika	July 2018	cobas Zika	Procleix Zika Virus Assay	For detection of Zika virus RNA in plasma specimens from individual living human donors, in whole blood and blood components and to screen organ and tissue donors.
HCV, HIV-1, HIV-2 and HBV	July 2018	NGI UltraQual Multiplex PCR Assay for HCV, HIV-1, HIV-2 and HBV	UltraQual Multiplex PCR Assay for HCV, HIV-1, HIV-2 and HBV Hepatitis B Virus	First assay to detect and differentiate HIV-2 from HIV-1. For the detection of HCV RNA, HIV-1 RNA, HIV-2 RNA, and HBV DNA in pooled and individual Source Plasma specimens.

Disease	Approved	Trade Name	Proper Name	Purpose or Benefit
Reversal of Factor Xa Inhibitors	May 2018	ANDEXXA	coagulation factor Xa (recombinant), inactivated-zhzo	For patients treated with rivaroxaban and apixaban, for reversal of anticoagulation due to life-threatening or uncontrolled bleeding.

FUNDING HISTORY[52]

Fiscal Year	Program Level	Budget Authority	User Fees
FY 2016 Actual	$329,156,000	$215,308,000	$113,848,000
FY 2017 Actual	$340,016,000	$215,443,000	$124,573,000
FY 2018 Actual	$381,890,000	$217,135,000	$164,755,000
FY 2019 Annualized CR	$379,144,000	$217,138,000	$162,006,000
FY 2020 President's Budget	$431,561,000	$262,138,000	$169,423,000

BUDGET REQUEST

The FY 2020 Budget Request for the Biologics Program is $431,561,000, of which $262,138,000 is budget authority and $169,423,000 is user fees. This level provides a net increase of $52,417,000. Budget authority increases by $45,000,000 compared to the FY 2019 Annualized Continuing Resolution level and user fees increase by $7,417,000. The Center for Biologics Evaluation and Research (CBER) amount in this request is $387,812,000. The Office of Regulatory Affairs amount is $43,749,000.

The FY 2020 Budget allows the Biologics Program to advance public health through innovative regulation that promotes the safety, purity, potency, effectiveness, and timely delivery of biological products to the American public. FDA will continue to expedite the use of advanced technologies and methods to facilitate product development, such as newly identified clinical biomarkers, innovative clinical trial designs, for a broad range of complex and life-threatening diseases.

FDA will work to reduce review times and regulatory burden by enhancing FDA-sponsor communications in its user fee programs and continuing to use FDA's expedited programs such as the RMAT Designation, Fast Track, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review to expedite the approval and availability of important products for patients, when appropriate. These pathways will help expedite the development and review of innovative biological products, many of which address unmet medical needs in patients with rare, serious, or life-threatening conditions without compromising FDA's high standards for demonstrating the safety, efficacy, and quality of new medicines.

Through FDA's mission, the Agency will continue to protect the public against the threats of emerging infectious diseases and bioterrorism, including facilitating the development of

[52] Numbers reflect comparability adjustments for FY 2018, FY 2019, and FY 2020 consistent with budget figures.

prophylactic and therapeutic biologics and vaccines. Infectious diseases are not only spreading faster; they appear to be emerging more quickly than ever before. Since the 1970s, over 40 infectious diseases have been discovered. The regulatory science and research program will continue to engage in forward-looking priority setting to allocate its resources towards efforts that best support FDA's ability to respond to current and emerging public health needs and meet ever-changing scientific and technological advancements. This program has helped CBER keep pace with the tremendous scientific advancements being made in the field.

FDA collaborates and establishes relationships with other regulators and health agencies in the U.S. and throughout the world to respond quickly to public health threats resulting from outbreaks of emerging infectious diseases, pandemic influenza, and terrorism. This collaboration helps facilitate global access to vaccines and biological products that address critical health needs, including promoting research and sharing information to address global diseases and emerging threats impacting human populations. FDA also strategizes to harmonize existing regulatory standards and works with international scientific efforts to establish and maintain reference materials and standards for biologics.

FDA will advance the use of real-world evidence including through use of large databases from healthcare providers, insurers, and other partners, to identify safety problems associated with biologic product use in a cost-effective and rapid manner. The use of real-world evidence captured throughout the totality of a product's post-approval lifecycle has been a significant aid in informing regulatory decisions, including the development of new products and changes to existing products.

BUDGET AUTHORITY

Medical Product Safety (+$45 million / 20 FTE)

Integrated Pathogen Reduction of the Blood Supply: +$20.0 million / 4 FTE

Center: +$20.0 million / 4 FTE

This funding would allow CBER to create a pilot program for pathogen inactivation technology which could help protect the blood supply from existing and emerging pathogens and potentially reduce or eliminate donor deferral and/or testing requirements. This project would optimize adaptation of existing technology for pathogen reduction and implement a moderately-sized pilot program to assess the feasibility of the widespread introduction of pathogen inactivation of all whole blood that is collected. The request would facilitate necessary preparatory laboratory work, purchase of the necessary equipment, and contracting for the blood banking services and clinical trials required for the demonstration of the feasibility of this approach.

Bacterial contamination of platelets is a leading risk of infection from blood transfusion. Bacterially contaminated platelets are associated with a higher risk of morbidity and mortality than any other transfusable blood component and are an example where these technologies can dramatically help the American public.

Existing and emerging infectious diseases present a continued risk to blood safety, as they are spreading faster and emerging more quickly. Continued vigilance against emerging threats is critical, including the introduction of new technologies to keep the blood supply safe in the event of rapidly emerging novel pathogens. Pathogen reduction technologies applied to whole blood that is then separated into red cells, platelets, and plasma could help ensure that the entire blood

supply continues to be safe in the face of existing and emerging pathogens and could also reduce cost while ensuring availability even in the face of emerging pathogens.

Medical Countermeasures Initiative (MCMi): +$2.0 million / 8 FTE

Center: +$2.0 million / 8 FTE

This funding would improve and sustain the FDA's ability to foster the establishment of clear, scientifically supported regulatory pathways for MCMs as well as to fill critical scientific gaps and advance platform and manufacturing technologies to facilitate the efficient development and availability of MCMs. In addition, it will help bolster FDA staffing to support MCM-related work, in particular regulatory review capacity and expertise in the medical review divisions responsible for evaluating MCMs, so that development programs move forward efficiently, and that the FDA is better prepared to handle the demands of responding to CBRN and emerging threats.

Promote Domestic Manufacturing: $10.0 million / 4 FTE

Center: +$10 million and 4 FTE

The FY 2020 Budget increase will allow FDA to support new efforts to foster more investment and innovation in the development and creation of more modern, domestically-based manufacturing to improve the agility, flexibility, cost and reliability of manufacturing processes. This includes advanced manufacturing of biological products, including vaccines and cell- and gene-based therapies. With these manufacturing platforms, vaccine supply can be more easily ramped up on short notice, and certain vaccines can be rapidly modified to address infectious diseases, such as the flu. By developing a science-based framework that provides clarity for how products developed in these systems will be evaluated, and by funding research, development and testing of the enabling technologies, the agency can help reduce the cost and uncertainty of adopting these new manufacturing platforms, essentially de-risking them for adoption by industry.

Create a New Medical Data Enterprise: $13.0 million / 4 FTE

Center: +$13 million and 4 FTE

The FDA will advance the use of real-world experience to better inform patient care and provide more efficient, robust and potentially lower-cost ways to develop clinical information that can inform product review and promote innovation. The FDA will establish a new capability, including the development of data and analytical tools, to conduct near-real-time evidence evaluation. The FDA will also further explore the use of natural language processing and artificial intelligence to rapidly process information such as adverse event reports, allowing signal detection.

Expanding the FDA's capacity to utilize real-world evidence to evaluate the pre- and post-market safety and effectiveness of medical products would potentially generate processes that could improve the efficiency of the regulatory process, better inform patients and providers about pre- and post-market safety, reduce some of the burdens that drive up the time and cost required to bring beneficial innovations to the market and address barriers that can make certain important safety and effectiveness information around the real-world use of products hard to collect and evaluate.

USER FEES

Current Law User Fees: +$7.4 million

Center: +$7.5 million / Field: -$0.1 million

The Biologics Program request includes an increase of $7,417,000 for user fees authorized under FDARA, which will allow FDA to fulfill its mission of promoting and protecting the public health by ensuring safety and efficacy of medical products and accelerating innovation in the industry.

PERFORMANCE

The Biologics Program's performance measures focus on biological product review, manufacturing diversity and capacity for influenza vaccine production, strengthening detection and surveillance of FDA-regulated products and postmarket inspections to ensure the safety, purity, potency, and effectiveness of biological products, as detailed in the following table.

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2019 Target	FY 2020 Target	FY 2020 +/- FY 2019
233207: Review and act on standard New Molecular Entity (NME) New Drug Application (NDA) and original BLA submissions within 10 months of the 60 day filing date. *(Output)*	FY 2017: 100% Target 90% (Target Exceeded)	90%	90%	Maintain
233208: Review and act on priority NME NDA and original BLA submissions within 6 months of the 60 day filing date. *(Output)*	FY 2017:100% Target 90% (Target Exceeded)	90%	90%	Maintain
233205: Complete review and action on complete blood bank and source plasma BLA submissions within 12 months after submission date. *(Output)*	FY 2017: 100% Target 90% (Target Exceeded)	90%	90%	Maintain
233206: Complete review and action on complete blood bank and source plasma BLA supplements within 12 months after submission date. *(Output)*	FY 2017: 99.5% Target: 90% (Target Exceeded)	90%	90%	Maintain
233211: Review and act on new non-user fee, non-blood product applications within 12 months of receipt. *(Output)*	FY 2017: 100% Target: 60% (Target Exceeded)	60%	60%	Maintain

Measure	Year and Most Recent Result / Target for Recent Result (Summary of Result)	FY 2019 Target	FY 2020 Target	FY 2020 +/- FY 2019
234101: Increase manufacturing diversity and capacity for influenza vaccine production. *(Output)*	FY 2018: Continued evaluation of new methods to produce high-yield influenza vaccine reference strains. (Target Met)	Continue evaluation of new methods to produce high-yield influenza vaccine reference strains	Continue evaluation of new methods to produce high-yield influenza vaccine reference strains	Maintain
231301: Percentage of Lot Distribution Reports that were entered into the Regulatory Management System - Biologics License Applications (RMS-BLA) within 7 Days.	FY 2018: 100% Target 85% (Target Exceeded)	85%	85%	Maintain
234221: Percentage of Biologics significant inspection violations which receive appropriate follow-up after regulatory action was taken. (Output)	Baseline: 75% (New Measure)	70%	70%	Maintain
234222: Percentage of Biologics follow-up inspections conducted due to regulatory action on significant inspection violations that moved toward compliance. (Outcome)	Baseline: 71% (New Measure)	65%	65%	Maintain

Influenza Performance Measure

This performance measure supports the Department's national preparedness efforts in combating seasonal influenza, by increasing manufacturing diversity and capacity for influenza vaccine production. In FY 2018, FDA met the target to continue evaluation of new methods to produce high-yield influenza vaccine reference strains. Activities to meet this target included the following:

FDA continued efforts to develop new methods for determining influenza vaccine potency, an important component in the evaluation of high-yield influenza vaccine viruses. A third international collaborative study comparing several alternative methods was completed in FY18. This study demonstrated that some alternative methods were sensitive to the methods used for inactivating the potency reference standard and suggested that additional criteria be defined for the selection of reagents to be included in new assays. Additional follow-up studies are being planned for FY 2019 that will continue to evaluate and compare alternative potency methods.

FDA continued work to develop improved candidate vaccine viruses. FDA produced a new influenza candidate vaccine virus (CBER-RG7C) for the high pathogenic H7N9 A/Guangdong/17SF003/2016 virus recently isolated from an infected human in China. The hemagglutinin (HA) antigen yield was further optimized by targeted mutations in the HA gene. The optimized vaccine virus, CBER-RG7D, shown much higher viral protein yields than those of CBER-RG7C virus (increased by 90 percent in cells and 150 percent in eggs). Both vaccine viruses are listed at WHO website: http://www.who.int/influenza/vaccines/virus/candidates_reagents/summary_a_h7n9_cvv_20181108.pdf?ua=1, and can be used for manufacturers to produce inactivated vaccines against highly pathogenic A/Guangdong/17SF003/2016 -like influenza viruses.

New ORA Field Performance Measures

ORA is embarking on an initiative to move from output focused performance goals such as inspection counts to public health outcome-based performance goals. This initiative seeks to provide more meaningful performance goals for internal and external stakeholders, and to showcase more direct public health impacts for ORA. The new performance goals introduced for FY 2019 measure topics such as our commitment to follow-up on firms receiving significant inspection violations, as well as measurements related to ORA regulatory impact on violators, and are tracked on a 3-year rolling basis. Due to the nature of regulatory actions and subsequent follow-up conducted by FDA, the duration of these events can vary considerably. After regulatory action, FDA also works to schedule follow-up after a reasonable time has passed to allow the firm to correct for the original violations. A 3-year rolling timeline also ensures tracking of all significant violations that require attention and allows for a more robust analysis.

PROGRAM ACTIVITY DATA

CBER Workload and Outputs	FY 2018 Actual	FY 2019 Estimate	FY 2020 Estimate
Original Biologics License Applications (BLA)			
Workload [1]	21	21	21
Total Decisions [2]	58	58	58
Approved	46	46	46
BLA Efficacy Supplements			
Workload [1]	21	21	21
Total Decisions [2]	16	16	16
Approved	13	13	13
BLA Manufacturing Supplements			
Workload [1]	1,181	1,181	1,181
Total Decisions [2]	1,368	1,368	1,368
Approved	1,266	1,266	1,266
BLA Labeling Supplements			
Workload [1]	193	193	193
Total Decisions [2]	142	142	142
Approved	117	117	117
Original New Drug Application (NDA)			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0
NDA Efficacy Supplements			
Workload [1]	1	1	1
Total Decisions [2]	0	0	0
Approved	0	0	0
NDA Manufacturing Supplements			
Workload [1]	18	18	18
Total Decisions [2]	18	18	18
Approved	16	16	16
NDA Labeling Supplements			
Workload [1]	4	4	4
Total Decisions [2]	4	4	4
Approved	4	4	4
Original Abbreviated New Drug Application (ANDA)			
Workload [1]	0	0	0
Total Decisions [2]	1	1	1
Approved	1	1	1
ANDA Efficacy Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0

CBER Workload and Outputs	FY 2018 Actual	FY 2019 Estimate	FY 2020 Estimate
ANDA Manufacturing Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0
ANDA Labeling Supplements			
Workload [1]	0	0	0
Total Decisions [2]	0	0	0
Approved	0	0	0
Device 510Ks			
Workload [1]	54	54	54
Total Decisions [2]	64	64	64
Final Decision - SE	45	45	45
Device Premarket Applications (PMA)			
Workload [1]	3	3	3
Total Decisions [2]	8	8	8
Approved	2	2	2
Device Premarket Applications (PMA) Supplements			
Workload [1]	70	70	70
Total Decisions [2]	85	85	85
Approved	18	18	18
Investigational New Drugs (IND)			
Receipts: IND (new)	676	676	676
Receipts: IND Amendments	12,085	12,085	12,085
Total Active IND [3]	2,850	2,850	2,850
Investigational Device Exemptions (IDE)			
Receipts: IDE (new)	13	13	13
Receipts: IDE Amendments	353	353	353
Total Active IDE [3]	161	161	161
Patient Safety			
Adverse Event Reports Received [4]	78,266	80,000	85,000
Biological Deviation Reports Received	46,971	50,000	50,000
Sponsor Assistance Outreach			
Meetings	525	525	525
Final Guidance Documents [5]	33	30	30
Admin/Management Support			
Advisory Committee Meetings Held	9	13	13
FOI Requests Processed	268	320	320

[1] Workload includes applications received and filed.

[2] Total Decisions include approved, denied, withdrawn, approvable, approvable pending inspection, not approvable, exempt, major deficiency, substantially equivalent (SE), not substantially equivalent (NSE), de novo and complete response (CR).

[3] Total Active includes investigational applications received and existing applications for which CBER has received at least one amendment (IND) or supplement (IDE) during the FY being reported.

[4] Includes MedWatch, Foreign reports and VAERS reports. Does not include Fatality Reports or Medical Device Reports for CBER-regulated medical devices.

[5] Includes all FDA final guidances issued by CBER and other FDA centers that pertain to biological products.

Field Biologics Program Activity Data (PAD)

Field Biologics Program Activity Data (PAD)			
Field Biologics Program Workload and Outputs	**FY 2018 Actuals**	**FY 2019 Estimate**	**FY 2020 Estimate**
FDA WORK			
DOMESTIC INSPECTIONS			
UNIQUE COUNT OF FDA DOMESTIC BIOLOGICS ESTABLISHMENT INSPECTIONS	***1,849***	***1,892***	***1,892***
Bioresearch Monitoring Program Inspections	75	100	100
Blood Bank Inspections	807	900	900
Source Plasma Inspections	243	190	190
Pre-License, Pre-Market Inspections	81	55	55
GMP Inspections	45	28	28
GMP (Device) Inspections	13	7	7
Human Tissue Inspections	625	650	650
FOREIGN INSPECTIONS			
UNIQUE COUNT OF FDA FOREIGN BIOLOGICS ESTABLISHMENT INSPECTIONS	***70***	***47***	***47***
Bioresearch Monitoring Program Inspections	15	11	11
Foreign Human Tissue Inspections	1	0	0
Blood Bank Inspections	7	7	7
Pre-License, Pre-market Inspections	6	7	7
GMP Inspections (Biologics & Device)	38	20	20
TOTAL UNIQUE COUNT OF FDA BIOLOGIC ESTABLISHMENT INSPECTIONS	***1,919***	***1,939***	***1,939***
IMPORTS			
Import Field Exams/Tests	73	45	45
Import Line Decisions	170,575	179,104	188,059
Percent of Import Lines Physically Examined	0.04%	0.03%	0.02%
GRAND TOTAL BIOLOGICS ESTABLISHMENT INSPECTIONS	***1,919***	***1,939***	***1,939***

[1]ORA is currently evaluating the calculations for future estimates.